PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PZ02108 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/05574	19.12.2003	20.12.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K51/04		
Applicant		
AMERSHAM PLC et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.06.2004	18.05.2005
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/05574

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-19 as originally filed

Claims, Numbers

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☐ claims Nos.

   because:

   ☒ the said international application, or the said claims Nos. 14 in relation to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-5, 8-14 partially

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-5 complete, 8-14 partially .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5,8,10-14
	No:	Claims	9
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5, 8-14
Industrial applicability (IA)	Yes:	Claims	1-5,8-13
	No:	Claims	14 see separate sheet

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

In the present application, the International Searching Authority has restricted the search under the following objections under Articles 5 and 6 PCT:

Claims 1-5, 8-14 encompass a genus of compounds defined only by their function "linker", "tracer", "protecting group" wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

The fact that one could have assayed a compound of interest using the described assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (**other than those that might be particularly disclosed in an application**) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

Therefore, claims 1-5, 8-14 do not fulfil the requirements of Art. 5 and Art. 6 PCT.

Support in relation to the first invention is only to be found in the present application for those parts relating to the compounds explicitly disclosed by chemical name in the examples and in claims 2-5 excluding the vague term "protecting group"; the linkers as mentioned in the description at page 6, line 10- page 7 line 5; and the protecting groups as mentioned at page 7, line 15- page 8, line 2.

No international Preliminary Examination will be carried out in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

Re Item IV
Lack of unity of invention

This Authority considers that the present application lacks of unity (Rule 13.2 PCT), the reasons for the objection being as follows:

The problem underlying the present application is the improvement in synthetic methods for introducing 18F, in particular to obtain 18F labelled tracers for clinical use (see page 1, lines 13-15).

As solution to this problem several processes comprising treatment of a solid support-bound precursor with a source of 18F to produce the labelled tracer are proposed.

The common feature linking the different inventions together is the presence of the solid support linked to the precursor in the method of preparation of the radiolabeled tracer.

Prior art documents already address the problem of obtaining 18F labelled tracers for clinical use by a process comprising the treatment of a solid support-bound precursor with a source of 18F to produce the labelled tracer:

WO 02070020 (document D2) discloses the preparation of radiolabelled haloaromatics via polymer-bound intermediates by a process comprising the treatment of a solid support-bound precursor with a radiohalide ion including 18F to produce the labelled tracer wherein the precursor molecules are linked to the polymer support via a Sn (R1)2 group (see page 3, lines 1-10; claims 1, 16, 19, 22)

WO 9918053 (document D3) discloses the preparation of radiolabelled haloaromatics via polymer-bound intermediates. The document shows a process comprising the treatment of a solid support-bound precursor with a suitable radiohalide ion (term encompassing 18F) to produce the labelled tracer. The precursor molecules are linked to the polymer support via a Sn (R1)2 group (see page 3, claim 1)

Sutcliffe J. L. et al in Bioorganic & Medicinal chemistry letters (2000), vol. 10, pp. 1501-1503 (document D1). This document teaches the solid phase synthesis of 18F labelled peptides in which the precursor peptides are linked to polyethylene glycol-polystyrene support via a xanthen-2-oxovalerate linker (XAL). The reaction with 18F fluorobenzoic acid followed by cleavage of the radio tracer peptide from the solid support is rapidly achieved (see page 1502, col 2; figure 1).

For these reasons the technical feature mentioned above can no longer be accepted as linking the different inventions together.

Although presented under graphically similar tracer formulas, the chemistry involved for the different options of X group and tracers claimed as well as the reactions involved for each of them (nucleophilic vs. electrophilic) in the claimed processes are clearly distinguishable from each other a priori.
Furthermore as the single general inventive concept relies on the process of radiolabelling on a solid support-bound precursor, the selected tracer does not contribute as essential technical feature of the process as claimed.

As there is no other technical feature which could fulfil the role of special technical feature in the sense of rule 13.2 PCT, the present application lacks unity of invention, containing the following subjects.

1. Claims: 1-5 complete; 8-14 partially

   A process for the production of an 18F labelled tracer which comprises treatment of a solid support-bound precursor of formula I with 18F to produce the labelled tracer of formula II as depicted in claim 1. The compound of formula Ia per se. Pharmaceutical kit and cartridge for the preparation of

said 18F labelled tracer of formula II. Use of the kit or cartridge in positron emission tomography (PET). Excluding the subject matter of invention 2.

1.1. Claims: 2, 3 complete; 1, 8-14 partially

A process for the production of an 18F labelled tracer which comprises treatment of a solid support-bound precursor of formula Ia with 18F to produce the labelled tracer of formula IIa as depicted in claim 2. The compound of formula Ia per se. Pharmaceutical kit and cartridge for the preparation of said 18F labelled tracer of formula IIa. Use of the kit or cartridge in positron emission tomography (PET).

1.2. Claims: 4, 5 complete; 1, 8-14 partially

A process for the production of an 18F labelled tracer which comprises treatment of a solid support-bound precursor of formula Ib with 18F- to produce the labelled tracer of formula IIb as depicted in claim 4. The compound of formula Ib per se. Pharmaceutical kit and cartridge for the preparation of said 18F labelled tracer of formula IIb. Use of the kit or cartridge in positron emission tomography (PET).

2. Claims: 6, 7 complete; 8-14 partially

A process for the production of an 18F labelled tracer which comprises treatment of a solid support-bound precursor of formula III with a source of 18F to produce the labelled tracer of formula IV as depicted in claim 6. The compound of formula III per se. Pharmaceutical kit and cartridge for the preparation of said 18F labelled tracer of formula IV. Use of the kit or cartridge in positron emission tomography

(PET). Excluding the subject matter of invention 1.

Note that all inventions mentioned under item 1, although not necessarily linked by a common inventive concept, could be searched without effort justifying an additional fee.

The applicant was informed that the search is the responsibility of the ISA under Chapter I of the PCT, the procedure before the ISA is closed and that there is no provision in the PCT for a review of or an appeal against the findings of the ISA, either by the ISA itself or by the IPEA.

An international search report has only been established for the subject matter of invention 1 as listed above.

No international Preliminary Examination will be carried out in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT) (I. e. invention 2 as listed above)

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claim 14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The applicant's attention is drawn to the fact that the present opinion expressed as to novelty, inventive step and industrial applicability refers only to matter for which an international search report has been drawn up.

The following documents (D) are referred to in this communication

D1: Bioorganic & Medicinal Chemistry Letters (2000), 10(14), 1501-1503
D2: WO-A-02070020
D3: WO-A-9918053
D4: US-A-4540648
D5: International Journal Of Peptide And Protein Research (1991), 37(5), 430-439
D6: WO-A-0114354
D7: WO-A-0216333
D8: WO-A-9742203
D9: US-A-5312592

Novelty (Article 33 (1) PCT)

The subject-matter of present claims 1-5, 8, 10-14 as defined under the first invention appears to be novel in the sense of Article 33(1) PCT.

No prior art document discloses A process for the production of an 18F labelled tracer which comprises treatment of a solid support-bound precursor of formula I with 18F to produce the labelled tracer of formula II as depicted in claim 1or a harmaceutical kit and cartridge for the preparation of said 18F labelled tracer and its use in positron emission tomography (PET).

The subject-matter of present claim 9 as defined under the first invention is not novel in the sense of Article 33(1) PCT

D4 discloses a benzothiazole compound encompassed by formula (I) of present claim 1 linked to a solid support (film) and containing a coupler component.
The alleged difference on the "film forming binder" or "coupler component" (see claims 1, 2; column 7, paragraph 2) on this document presented by the applicant is not considered to be a valid distinction from the claimed "linker" in its full and complete scope, thus rendering the subject matter of present claim 9 not novel.

Inventive step (Article 33 (2) PCT)

The subject matter of present claims 1-5, 8-14 cannot be considered as involving an inventive step for the following reasons:

The problem to be solved by the present application is the improvement in synthetic methods for introducing 18F, in particular to obtain 18F labelled tracers for clinical use (see page 1, lines 13-15)

As solution to this problem a process comprising treatment of a solid support-bound precursor of formula I with 18F to produce the labelled tracer of formula II as depicted in claim 1 as well as the compound of formula Ia per se are proposed. A pharmaceutical kit and cartridge for the preparation of said 18F labelled tracer of formula II and the use of the kit or cartridge in positron emission tomography (PET) are also encompassed.

Documents D2, which can be considered the closest prior art for the assessment of inventive step discloses the preparation of radiolabelled haloaromatics via polymer-bound intermediates by a process comprising the treatment of a solid support-bound precursor with a radiohalide including 18F to produce the labelled tracer wherein the precursor molecules are linked to the polymer support via a Sn (R1)2 group. Kits comprising the labelled compound and further including a filter to remove excess precursor or the polymeric side products are also described (see page 3, lines 1-10; claims 1, 16, 19, 22)

The difference between D2 and the subject matter of the present application is the fact that the particular tracer molecules as depicted by formula I in present claim 1 is not disclosed in these documents.

The skilled man, well aware that 18F has been incorporated into haloaromatics via the treatment of the corresponding solid support-bound precursor with a source of 18F to produce the labelled tracer, would have applied these known general processes and methods as an alternative of 18F labelling process in order to render 18F benzothiazole compounds encompassed by present formulas A, Aa, Aa1, Ab, Ab1, Ac, Ac1 which are known from D6 (see route D; page 18; claims 17, 24; examples 44, 45) and from D7 also for PET use (see structure D; claims 1, 2, 26, 34).

He would have been reinforced in his choice by the fact that many non-biological molecules as in the previously discussed documents D2, D3 or biological molecules as in D1 (see page 1501 col. 1) or D5 (see abstract) have been 18F labelled by processes comprising the treatment of the corresponding solid support-bound precursor with a source of 18F to produce the labelled tracer.

Furthermore the particular features of present claims 10-13 cannot either be considered as providing an inventive step to the subject matter of the present application, as kits for the preparation of radiopharmaceuticals including a de-ionizing column (see D9, claim 3) as well as a cartridge for solid phase deprotection of the resultant product (see D8, claims 1, 24) have been described.